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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/535,187 | 10/31/2005 | Dharmaraj Ramachandra Rao | TPP 31767 | 2383 |

24257 7590 05/03/2007

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| EXAMINER | |
|---|---|
| YOUNG, SHAWQUIA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1626 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 05/03/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/535,187 | RAO ET AL. | |
| | Examiner | Art Unit | |
| | Shawquia Young | 1626 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-15,17-20,22,23,25 and 27-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 1-15 is/are allowed.

6)☒ Claim(s) 17-20,22,23 and 27-30 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

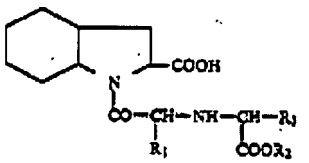
## DETAILED ACTION

Claims 1-15, 17-20, 22, 23, 25 and 27-30 are currently pending in the instant application. Applicants have cancelled claims 16 and 26 in an amendment filed on January 8, 2007.

## I. *Response to Arguments*

Applicant's arguments, filed January 8, 2007 with respect to the rejection of claim 23 under 35 USC 102(b) as being anticipated by Vincent et al (US Patent No. 4,508,729); the rejection of claim 25 under 35 USC 102(b) as being anticipated by Straub et al. (US Patent No. 6,932,983) and the rejection of claims 17-20 and 22 under 35 USC 103(a) as being unpatentable over Vincent et al. have been fully considered and are partially persuasive. The rejection of claim 23 under 35 USC 102(b) as being anticipated by Vincent et al (US Patent No. 4,508,729) and the rejection of claim 25 under 35 USC 102(b) as being anticipated by Straub et al. (US Patent No. 6,932,983) have been withdrawn.

Applicants traverse the use of Non-patent document X and non-patent document U as references listed in the form PTO-892. Applicants argue that these two references do not qualify as prior art under 35 USC 102. However, the Examiner wants to point out that these two references where used in support of the rejection under 35 USC 112, 1$^{st}$ paragraph which relates to enablement of certain claims in the instant application. Therefore, the references are not considered prior art but are just being used to support the Examiner's position.

Applicants traverse the rejection of claims 17-20 and 22 under 35 USC 103(a) as being unpatentable over Vincent et al (US Patent No 4,508,729). Applicants argue that Vincent et al. does not teach nor suggest the hydrated salt of perindropril. Applicants further state that there is no explicit disclosure in Vincent et al. of a salt of perindopril. However, the Examiner points out that claim 1 is drawn to an iminoacid compound having the formula  , wherein $R_1$ represents lower-alkyl having 1 to 4 carbons inclusive, $R_2$ represents hydrogen or lower-alkyl having 1 to 4 carbon atoms inclusive and $R_3$ is $-CH_2CH_2CH_3$, a salt thereof with a pharmaceutically acceptable inorganic or organic base, and an addition salt thereof with a pharmaceutically acceptable inorganic or organic acid. Claim 3 is drawn to (2S)-1-{N[(1RS)-1-ethoxycarbonylbutyl]-(S)-alanyl}-2-carboxyperhydroindole (perindopril), its (S)-isomer or the sodium salt of these. Therefore, the salt of perindropil is being claimed in the original patent.

Applicants have failed to show any unexpected results that occur when using the hydrated form of perindopril or any differences when comparing perindopril with the hydrated form of perindopril in the original disclosure. Therefore, as mentioned in the previous Office action, it is well established that "something which is old does not become patentable upon the discovery of a new property". In re Grasselli, 713 F. 2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983). The rejection of claims 17-20 and 22 under 35 USC 103(a) as being unpatentable over Vincent, et al. (4,508,729) has been

maintained. However, upon further examination of the current amendments to the claims, a new ground(s) of rejection is made in view of claims 23 and 27-29 under 35 USC 103(a) as being unpatentable over Vincent, et al. and a rejection of claim 30 under 35 USC 112, 1st paragraph, enablement.

## III. *Rejection(s)*

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

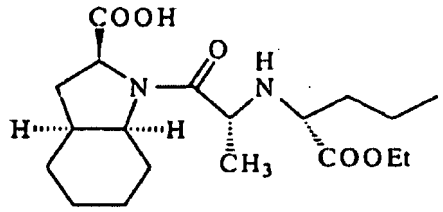
*Graham v. John Deere Co.* set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a). *See Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23 and 27-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Vincent, et al.* (4,508,729, 1985). It is well established that

"something which is old does not become patentable upon the discovery of a new property". In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

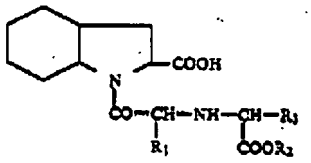
Applicants claim a pharmaceutically composition comprising a pharmaceutically acceptable salt of perindopril according to claim 17 with the structure



$^{n}H_2O$ wherein n is an integer of 1 to 5, or a reciprocal of integers 2 to 5, together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

***The Scope and Content of the Prior Art (MPEP §2141.01)***

The *Vincent, et al.* reference teaches substituted iminodiacid compounds and the salts thereof with the genus structure



wherein $R_1$ represents lower-alkyl having 1 to 4 carbons inclusive, $R_2$ represents hydrogen or lower-alkyl having 1 to 4 carbon atoms inclusive and $R_3$ is $-CH_2CH_2CH_3$. One of the species taught by *Vincent, et al.* is the sodium salt of (2S)-1-{N[(1RS)-1-ethoxycarbonylbutyl-(S)-alanyl}-2-carboxyperhydroindole (See claim 3). Claim 5 is drawn to a pharmaceutical composition containing as active ingredient a compound according to claim 3, in conjunction with an inert, non-toxic pharmaceutically-acceptable carrier or excipient.

***The Difference Between the Prior Art and the Claims (MPEP §2141.02)***

The difference between the prior art of *Vincent, et al.* and the instant invention is that the applicants are claiming a pharmaceutical composition comprising the hydrated form of a pharmaceutically acceptable salt of perindopril whereas the prior art teaches a pharmaceutical composition comprising pharmaceutically acceptable salt of perindopril.

***Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)***

In In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983), it was well established that something which is old does not become patentable upon the discovery of a new property. Adding water to a well-known product via hydration, does not make the claim patentable without showing unexpected results. Also, the reference teaches a pharmaceutical composition comprising the claimed compound and a pharmaceutically acceptable carrier or excipient. Water meets the limitation of pharmaceutical acceptable carrier and therefore a hydrated form of a pharmaceutically acceptable salt of perindopril will be present in the pharmaceutical composition. The motivation to optimize the compounds and process of *Vincent, et al.* would be to prepare similar compounds that have similar pharmacological properties, i.e. ACE inhibitors useful in treating cognitive disorders. Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to optimize the compounds of *Vincent, et al.* and isolate the hydrated form of a pharmaceutically acceptable salt of perindopril.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case,

***The nature of the invention***

The nature of the invention of claim 30 is a method for inhibiting ACE in a patient in need.

***The state of the prior art and the predictability or lack thereof in the art***

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art

would recognize that in regards to therapeutic effects of cognitive disorders by inhibiting ACE would make a difference.

Applicants are claiming methods of inhibiting ACE in a patient in need. Further, applicants fail to identify diseases or disorders that can be treated by inhibiting ACE by using the claimed invention.

Applicants' claims are therefore drawn to a method of inhibiting ACE in a patient in need, a pharmaceutical composition comprising an effective ACE inhibitory amount of claimed products, and a method of manufacturing a medicament for inhibiting ACE. Various diseases and disorders (i.e. hypertension, cognitive disorders, cardiovascular disorders, etc.) can be treated by ACE inhibitors (See e.g. Das, 2005). Enablement for the scope of treating cognitive disorders and cardiovascular disorders by inhibiting ACE is not present in the specification. Cardiovascular disorders include hypertension, stroke, congestive heart failure, etc. Cognitive disorders include conditions such as delirium, Alzheimer's disease, Pick's disease, Parkinson's disease, Binswanger's disease, etc.

(URL:http://en.wikipedia.org/wiki/Category:Cognitive_disorders)

Furthermore, there is a vast range of causes for the problem and biochemical pathways that mediate cognitive disorders that affect the various nervous systems. There is no common mechanism by which all, or even most, cognitive disorders arise and one treatment cannot be used to treat all types of cognitive disorders.

Applicants' claims are therefore drawn to the treatment of Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease

and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html.)

In addition, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents (*See* e.g., the Cecil Textbood of Medicine, 20th edition (1996), Vol. 2, page 1994).

Applicants are also claiming a treatment of stroke. Stroke represents on of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics

and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Hence, in the absence of a showing of correlation between all the diseases encompassed by the claims as capable of treatment by inhibiting ACE one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of preventing neuronal death and, for example, since it is no known cure for Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

***The amount of direction present and the presence or absence of working examples***

The only direction or guidance present in the instant specification is the listing of several diseases applicant considers as treatable by the claimed invention found on pages 1 and 7. There are no working examples present for the treatment of any disease or disorder by inhibiting ACE.

Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

***The breadth of the claims***

The breadth of the claims is drawn to a method for inhibiting ACE in a patient in need.

***The quantity of experimentation needed***

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all conditions such as cognitve disorders, hypertension, etc. would be benefited by the inhibition of ACE would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

***The level of the skill in the art***

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention in a method of inhibiting ACE. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the method claims.

## IV. Objections

***Specification***

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the abstract contains the term “said”. Correction is required. See MPEP § 608.01(b).

## V. Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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